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(19)(CA) **CANADIAN PATENT** (12)

(54) Therapeutic Agent for Skin Ulcers

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ABSTRACT OF THE DISCLOSURE

The present invention provides a novel therapeutic agent for skin ulcers comprising a therapeutically effective amount of adenosine-3',5'-cyclic phosphate or a derivative thereof, as the active ingredient, in association with a pharmaceutically acceptable carrier therefor; and also a method for the treatment of skin ulcers by using this agent. The therapeutic agent is prepared into various forms such as emulsions, ointments and creams, and is externally applied to the affected part.

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BACKGROUND OF THE INVENTION

1) Field of the Invention

This invention relates to a novel therapeutic agent for skin ulcers.

2) Description of the Prior Art

As skin ulcers generally mentioned are pressure gangrenes caused from circulation disorders due to pressure suffered for a long period; gangrenes derived from diabetes or cerebral infarction; thermal burns; frostbites; radionecrosis and so on.

These skin ulcers are difficult to heal once they occur. Treatments currently carried out are internal treatments in which antibiotics, kallikrein, anginin [pyridinol carbamate (Banyu)], nicotinic acid or antiphlogistic protease preparations are administered locally or totally, and surgical treatments in which disinfectants, steroid hormones, antimicrobial preparations and the like are externally applied.

Internal administrations, however, sometimes fail to give an expected improvement because only a part

of the administered medicine reaches and acts on the affected part. Besides, they cannot avoid side effects produced. From these reasons, external preparations would be advisable. However, few medicines were known to be effective which could directly act on the skin and heal the affected part. This has made the treatment of skin ulcers difficult.

SUMMARY OF THE INVENTION

Under the above situation, the present inventors have earnestly carried out studies in order to provide an external preparation effective for healing skin ulcers, and have found that adenosine-3',5'-cyclic phosphate (hereafter may be referred to as "c-AMP") or its derivatives are very effective. The present invention was accomplished based on the above finding.

Accordingly, this invention provides a therapeutic agent for skin ulcers comprising a therapeutic agent for skin ulcers comprising a therapeutically effective amount of adenosine-3',5'-cyclic phosphate or a derivative thereof as the active ingredient, in association with a pharmaceutically acceptable carrier therefor.

The present invention also provides the use of adenosine-3',5'-cyclic phosphate or a derivative thereof in a therapeutically effective amount for application to skin ulcers.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

c-Amp derivatives usable in this invention

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include N^6-monoacyladenosine-3',5'-cyclic phosphate, 2'-O-monoacyladenosine-3',5'-cyclic phosphate, N^6,2'-O-diacyladenosine-3',5'-cyclic phosphate or their 8-mercapto, 8-lower alkylthio, 8-benzylthio, 8-amino, 8-hydroxy, 8-chloro or 8-bromo derivatives, 8-benzylthioadenosine-3',5'-cyclic phosphate or its N^6-lower alkyl derivatives or 8-mercaptoadenosine-3',5'-cyclic phosphate. c-AMP and these derivatives are all known compounds which are described in Japanese Patent Publication (Tokkyo Kokoku) No. 22559/1975, "Nippon Rinsho", vol. 40, No. 11, pp 14-19, 1982, Journal of Cyclic Nucleotide Research, 2, pp 307-319(1976) and Biochim. Biophys. Acta, 148 (1967), 99-105.

The therapeutic agents for skin ulcers according to this invention can be prepared into various forms such as solutions, emulsions, ointments, creams, lotions, poultices and the like by incorporating c-AMP or its derivatives into a base. As to the base, any known base materials are usable. Preferable preparations are solutions obtained by dissolving c-AMP or its derivatives in a physiological saline solution and ointments using macrogol as a base. The amount of c-AMP or its derivatives to be incorporated is varied in a wide range, and normally, 3 wt% of the quantity of the

base is preferable.

The therapeutic agents according to this invention are generally applied to the affected part from once to several times a day, each time in such an amount that c-AMP or its derivatives are contained 3 mg - 3 g /100cm^2 and more preferably 50 - 1000 mg/100cm^2 depending on the degree and area of ulceration.

This invention is now explained in more detail by way of examples, which should not be construed as limiting the invention.

Example 1

(1) A solution was prepared by dissolving 300 mg of sodium bucladesinate (N^6,2'-O-dibutyryladenosine 3',5'-cyclic sodium phosphate) in 10 mg of physiological saline solution.

(2) An ointment was prepared by using 50 g of Macrogol 4000, 50 g of Macrogol 400 and 3 g of sodium bucladesinate in a usual manner.

Example 2

A 60 year old male patient who was diagnosed as having pyoderma gangrenosum in the lower part of the left thigh was treated with various ointments, pig skin

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applications, intravenous drip and the like, but there were no significant improvements observed.

This patient was then treated with 5 mg sodium bucladesinate solution (content of sodium bucladesinate: 150 mg) obtained in Example 1 (1) which was soaked in gauze and applied to the affected part once a day. A few days later, the ulceration area was observed to be reduced, and about 2 months later, the ulceration was completely epithelializated and healed.

Example 3

Several ulcers shown in Table 1 were treated using an ointment of sodium bucladesinate obtained in Example 1 (2). In each case, the ointment was applied to the affected part in such an amount that sodium bucladesinate was contained 50 - 1000 mg/100 cm^2.

The results are also shown in Table 1. The data indicate excellent therapeutic effects for all cases. In the table, the alphabet "w" means week.

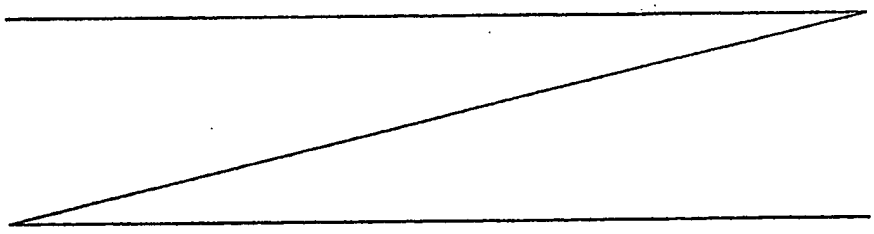

Table 1

Name	Sex	Age	Diagnosis	Basic Disease	Suffering Period	Prior Treatment	Symptoms	Administration Period	Progress	Side Effects	Effectiveness
I.M	f	86	Decubitus	Cervical carcinoma	About 1 month	About 1 month treatment by Gentacin Ointment [gentamicin C_{1a} (Schering/Shionogi)] found invalid. *Trademark	Ulceration with white coverings and faulty granulations in the lumbar region.	6w	After a few days of administration, the white coverings began to disappear and benign reddish granulations appeared; Ulceration area rapidly reduced to 14.0 (7.0 x 2.0)(1w), 4.5 (3.0 x 1.5)(2w) and 2.76 (2.3 x 1.2)(4w). After 6 weeks, epidermis was formed with thin crust remained partially and almost healed.	None	Very Effective
K.K	f	72	Decubitus	Rupture of the bladder; Peritonitis; Fracture of the lumbar vertebrae; Palsy in the left side	9 months	2 month treatment by "Hibitane" Cream [chlorhexidine (Sumitomo)], "Rinderon A" Ointment [fradiomycin sulfate, sodium betamethasone phosphate (Shionogi)] found invalid. 7 month treatment by Solcoceryl [deproteinized extract obtained from hemolysate of calves (Tobishi)], "Isalopan" ointment [aluminum chloroxy allantoinate (Grelan/Takeda)], Stable Trypure [trypsin (Kodama)] found invalid.	Ulcerations of 420 (20 x 21) in the lumbar region and 110.5 (13 x 8.5) in the femoral region; thigh bone, head thereof and ilac bone are partially exposed and the muscle appears old meat; Strong ischaemia; Systemic conditions very bad, terminal stage.	4w	After 1 week of administration, granulations turned to hemorrhagic and muscle color to fresh red. After 3 weeks, the ulceration area reduced to 360.0 (18 x 20) in the rear lumbar part and 85.0 (12.5 x 6.8) in the thigh (85.7% and 76.9%, respectively). 4w: Death from basic disease	None	Effective
T.I	m	37	Decubitus	Encephalopathy (Vegetation)	6 months	5 month treatment by Solcoceryl, "Elase C" [fibrinolysin, deoxyribonuclease (Sankyo)] revealed a little improvement. Thereafter, 1 month treatment by mercurochrome found invalid.	Deep ulceration of 2.7 (1.9 x 1.4) in the lumbar region; Granulations slightly faulty; Wound region tends to tear sideways because the patient strongly presses his lumber part to the floor when he changes the position of his upper part or lower part due to rigidity.	7w	After 3w of administration, granulations began to have very good appearance. Ulceration area reduced. 3w: 1.5 (1.9 x 0.8), 6w: 1.0 (2.0 x 0.5), 7w: 0.6 (1.6 x 0.4) = 22.2%	None	Effective

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Table 1 continued

Name	Sex	Age	Diagnosis	Basic Disease	Suffering Period	Prior Treatment	Symptoms	Administration Period	Progress	Side Effects	Effectiveness
Y. M.	m	57	Decubitus	Gastric ulcer; Peritonitis; Pulmonary insufficiency	2w	Treatment by "Isodine"* [povidone iodine (Meiji Seika)], excerbation *Trademark	Ulceration of 3.7 (1.6 x 2.3) in the lumbar region; Granulations slightly faulty	4w	After 1w, granulations turned to be dry, no exudate; after 2w, very good conditions; after 4w completely healed. Ulceration area: after 2w, 2.5 (1.3 x 1.9), after 3w; 1.0 (0.9 x 1.1), after 4w, completely healed.	None	Very Effective
R. S.	m	55	Ulceration from radiation	Left cervical tumor (squamous cell carcinoma); Hypertension Diabetes	about 2.5 months	Geben creaa [silver sulfadiazine (Tokyo Tanabe)], intractable	Ulceration with light yellow gelly substances in the left region of neck	1w	1w of administration brought significant reduction. Before Administration: 2.1 (2.1 x 1.0 cm) 1w: 0.19 (0.95 x 0.2 cm) = 9.0%	None	Very Effective
R. H.	f	7	Ambustion (II)	None	5w	5 weeks of treatment by Geben cream, no effect	Ulceration of 1.3 (1.3 x 1.0) in the right-lower thigh	2w	After 1w, 0.8 (0.6 x 0.3), dry, no exudate. After 2w, completely healed.	None	Very Effective

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Table 1 continu

Name	Sex	Age	Diagnosis	Basic Disease	Suffering Period	Prior Treatment	Symptoms	Administration Period	Progress	Side Effects	Effectiveness
H. K.	m	25	Ambustion II	None	2w	*Elase* ointment, Gentacin ointment external application of Fucidin Leo Intertulle [sodium fusidate (Sankyo)] by other hospital found invalid. Came to this hospital to have skin grafting *Trademark	Deep ulceration in side region of the right-lower thigh by a foot warmer. Partially blacken with dirty yellow coverings	6w	1w: dry, soft black crust removed; Ulceration definitely disappeared and skin grafting considered unnecessary. Prior to Administration: 5.6 (2.8 x 2.0 cm) 1w: 3.8 (2.4 x 1.6 cm) 2w: 1.3 (1.5 x 0.85 cm) 5w: 0.1 (0.4 x 0.2 cm) of erosion 6w: healed	None	Very Effective
O. S.	f	52	Leg ulcer	Iron deficiency anemia	about 2 months	Geben cream found invalid. "Elase C" found invalid.	Deep ulceration with white coverings in the inside of the left leg; Painful		1 day: dried 2 days circumferential erosion healed About 2w: dry crust Strong pain was suffered in the 1 st day and the pain decreased from the next day. After 2 weeks, pain almost disappeared. Prior to Administration: 2.5 (1.8 x 1.4 cm) 1w: 1.2 (1.0 x 1.2 cm) 2w: 1.0 (0.9 x 1.1 cm) 4w: 0.4 (0.5 x 0.8 cm), crust 6w: 0.2 (0.4 x 0.55 cm) Returned home but came back to the hospital again due to exacerbation caused by being frequently forced to maintain upright posture at home.	None	Effective
H. S.	m	27	Frostbite	None	1w	None	Blisters and blood blisters were formed in legs due to frostbite. No sense at all. Removal of Necrosis epidermis resulted in deep ulceration.	About 8w	1w: no exudate 2w: very shallow erosion, ulcer area reduced, sense come back again 4w: 1.0 x 0.75 cm 5w: dry erosion 8w: completely healed, normal sensation	None	Very Effective

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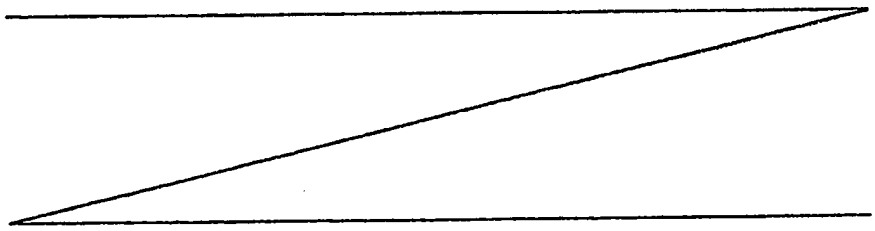
Example 4

Vulnerary effects of sodium bucladesinate and 8-benzylthio-N^6-butyladenosine-3',5'-cyclic phosphate (hereafter abbreviated to BTBcAMP) were investigated by the following test. The results are shown in Table 2.

Test Method

Several groups of SD male rats (8 weeks old, weighing 225 - 285 g), each group consisting of three rats, were used. The hair in the abdominal region was removed and then the local skin was excoriated to have a lesion of 3 cm in diameter under etherization to prepare a full-thickness avulsion model. Test samples were sodium bucladesinate and BTBcAMP. They were applied 60 mg each for the first day of the treatment, and 30 mg each for the second and the third day. The samples were applied as they were. The lesion area of each rat was measured after 0, 24, 48 and 72 hours respectively, and an average value of reduction ratio obtained was regarded as reflecting the vulnerary effect.



(Results)

Table 2

% Reduction in the full-thickness avulsion model

Time (hours)	0	24	48	72
Sample				
Control	-	4.9	13.7	13.5
Sodium Bucladesinate	-	2.4	12.5	20.3
BTBcAMP	-	15.3	17.9	21.4

From the above data, it is understood that the groups which were treated with sodium bucladesinate and BTBcAMP were rapidly healed compared with Control (No treatment carried out).

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A therapeutic agent for skin ulcers comprising a therapeutically effective amount of adenosine-3',5'-cyclic phosphate or a derivative thereof as the active ingredient, in association with a pharmaceutically acceptable carrier therefor.

2. A therapeutic agent for skin ulcers according to Claim 1 wherein said derivative of adenosine-3',5'-cyclic phosphate is N^6-monoacyladenosine-3',5'-cyclic phosphate, 2'-O-monoacyladenosine-3',5'-cyclic phosphate, N^6,2'-O-diacyladenosine-3',5'-cyclic phosphate or their 8-mercapto, 8-lower alkylthio, 8-benzylthio, 8-amino, 8-hydroxy, 8-chloro or 8-bromo derivatives, 8-benzylthioadenosine-3',5'-cyclic phosphate or its N^6-lower alkyl derivatives or 8-mercaptoadenosine-3',5'-cyclic phosphate.

3. A therapeutic agent for skin ulcers according to Claim 2, wherein the acyl group of said derivative is n-butyryl.

4. A therapeutic agent for skin ulcers according to Claim 1 wherein said derivative of adenosine-3',5'-cyclic phosphate is sodium N^6,2-O-dibutyryladenosine-3',5'-cyclic phosphate.

5. A therapeutic agent for skin ulcers according to Claim 1 wherein said derivative of adenosine-3',5'-cyclic phosphate is 8-benzylthio-N^6-butyladenosine-3',5'-cyclic phosphate.

6. A therapeutic agent for skin ulcers according to any one of Claims 1 to 5 wherein said agent is prepared in any form applicable externally.

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7. The use of adenosine-3',5'-cyclic phosphate or a derivative thereof in a therapeutically effective amount for application to skin ulcers.

8. Use of an adenosine-3',5'-cyclic phosphate or a derivative thereof for the production of a composition effective for the treatment of skin ulcers.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente